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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/125,460	08/19/98	WALDMANN	H 1283-36

EXAMINER

HM12/0515

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DANIEL, P

ART UNIT	PAPER NUMBER
1644	17

DATE MAILED: 05/15/01

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 3/5/01

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 2,6-11, 24, 25 is/are pending in the applicatic
Of the above, claim(s) 18-21, 24 is/are withdrawn from consideratio
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 2,6-17, 22, 25 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requireme

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

DETAILED ACTION

1. Applicant's amendment, filed 3/5/01 (Paper No. 16), is acknowledged.
Claims 1 and 3-5 have been canceled. Claim 23 has been canceled previously.
Claim 25 has been added.
Claims 2, 6, 7, 9, 13, 14, 16 and 17 have been amended.

Claims 2, 6-17, 22 and 25 are under consideration in the instant application.

Claims 18-21 and 24 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected in

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 3/5/01 (Paper No. 16).
The rejections of record can be found in the previous Office Action (Paper No. 15).

3. Formal drawings, filed 5/18/98, comply with 37 CFR 1.84.
Please see the form PTO-948 previously sent in Paper No. 15.

4. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.
Appropriate corrections are required

5. Claims 2, 6-17, 22 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Applicant has not disclosed how to make and use modified antibodies with reduced affinity for cell surface antigen which induce immunological tolerant to the therapeutic antibody. There is insufficient objective evidence to support the ability to make and use such modified antibodies to accomplish the claimed therapeutic endpoint of tolerance, encompassed by the claimed invention.

Applicant's arguments, filed 3/5/01 (Paper No. 16), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper No. 15

Applicant's reliance on applicant's own work as well as art known in vitro and animal experimental models are acknowledged.

Consistent with applicant's comments; it is acknowledged that when tolerance is achieved in the human, it will almost certainly be based on principles common to other species, including rodents.
Applicant asserts that the applicant's work is associated with tolerance to immunoglobulins rather than other situations, such as transplantation.

However, as applicant acknowledges in conjunction with Calne et al. (Lancet); achieving tolerance in humans is still for the future.

Applicant's assertions that it will be likely that tolerance will be induced in the absence of objective evidence stands in contrast to art known limitations of immunogenicity of therapeutic antibodies.

Applicant's reliance upon a number of techniques of modifying therapeutic antibodies which would have been well known to the skilled person at the time the invention was made is acknowledged.

In contrast to applicant's assertions; there has been widespread acceptance that there has been little future for the use of rodent monoclonal antibodies per se for in vivo human therapy and that repeated dosing with chimeric or humanized antibodies is limited by anti-idiotypic responses.

In contrast to applicant's assertions that such techniques for eliciting tolerance to therapeutic antibodies; applicant's own work and admissions are consistent with these art known observations that the various techniques to provide therapeutic antibodies that such techniques have been directed toward reducing the immunogenicity of therapeutic antibodies, which is distinguishable from inducing tolerance to said therapeutic antibodies.

Again, as pointed out previously; applicant is invited to consider alternative recitations that focus more on the structure of the claimed modified antibodies rather than their intended use currently recited of inducing tolerance.

The amendments must be supported by the specification so as not to add any new matter.

Applicant's arguments are not found persuasive.

6. Claims 2, 6-17, 22 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

Applicant has not provided direction and guidance as how to make and to use modified versions of therapeutic antibodies and fragments thereof which results in a reduced affinity for antigen from the pertinent therapeutic antibody.

Applicant's arguments, filed 3/5/01 (Paper No. 16), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper No. 15

Applicant argues in conjunction with reliance upon a number of art known techniques of modifying therapeutic antibodies that the present invention is based on successfully modifying therapeutic antibodies to reduce binding affinity in order to induce tolerance to therapeutic antibodies.

Applicant acknowledges that while many possibilities within the scope of the clams is possibly true; the embodiments are something that would have been in the ambit of the skilled artisan without the application of inventive ability and without undue burden.

In contrast to applicant's assertions; given the absence of structural elements in the claims (e.g. amino acid sequences, deposited antibodies) or disclosure of structural elements in the specification as filed; there is insufficient guidance and direction as to how to make and use the claimed modified antibodies encompassing modifications, both substantially the same sequences as well as alterations and substitutions. Such modified antibodies and their therapeutic antibody counterparts encompass structural elements which are not readily apparent in the instant application as filed. The instant specification indicates that it is desirable to start with a solved crystal structure, preferably one that is co-crystallized with antigen so that the key contact residues be identified and substituted (see page 14, paragraph 2). Here, it is noted that alternative means to achieving said modifications including good molecular models, CDR swapping experiments , alanine scanning mutagenesis and genetic techniques such as phage display.

However, minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. The claims not only encompass modified antibodies from ill-defined therapeutic antibodies and a myriad of cell surface specificities including a number of modifications including alterations, substitutions and substantially the same sequences involving nucleic acids and fragments thereof. For example, the claimed substitutions encompass single or double amino acid substitutions without providing clear guidance as to exactly where said substitutions would be made and how the skilled artisan would predict which therapeutic antibody may be changed accordingly. In the absence of sufficient information as to the structure-function relationship of the antibody-antigen interactions; it would require undue experimentation to practice the invention in a manner commensurate in scope with the claims, that is, to predict which of the innumerable modifications encompassed by the claimed invention would reasonably be expected to provide antibodies capable of inducing immunological tolerance to therapeutic antibodies.

Applicant has not provided sufficient biochemical information (e.g. amino acid sequence) nor has provide sufficient deposit information to enable the claimed therapeutic antibodies and, in turn, to enable the claimed modified versions of said therapeutic antibodies.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, the changes which can be made in the structure of therapeutic antibodies such that the modified versions of therapeutic antibodies and fragments thereof results in a reduced affinity for antigen from the pertinent therapeutic antibody and, in turn, provides or maintains sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue

Applicant's arguments are not found persuasive.

7. Claims 2, 6-17, 22 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's arguments, filed 3/5/01 (Paper No. 16), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper No. 15

Applicant relies upon experimental details of the production of certain modified in the instant application, including the Examples, to indicate that application was in possession of the claimed invention.

In contrast to applicant's assertions, the following of record is reiterated herein for applicant's convenience.

It is noted that this is a written description rejection rather than an enablement rejection under 35 U.S.C. 112, first paragraph.

The instant claims are drawn to modified antibodies including independent claim 1 which recites that the antibody is not a mixed molecule antibody having an H or L chain of the therapeutic antibody paired with and L or H chain of an unrelated antibody. Given the absence of structural elements in the claims (e.g. amino acid sequences, deposited antibodies); there is insufficient guidance and direction as to the written description of these modified antibodies encompassing modifications, both substantially the same sequences as well as alterations and substitutions. Such modified antibodies and their therapeutic antibody counterparts encompass structural elements such as sequences which do not meet the written description provision of 35 USC 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed modified antibodies or their therapeutic antibody counterparts and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.
Thus, the specification fails to describe these DNA sequences. The Court further elaborated that generic statements are not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. Finally, the Court indicated that while applicants are not required to disclose every species encompassed within a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, defined by nucleotide sequence, falling within the scope of the genus, See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Therefore, there is insufficient written description for the claims modified antibodies under the written description provision of 35 USC 112, first paragraph.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant's arguments are not found persuasive.

8. Claim 10: It is apparent that the CAMPATH-1 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Applicant's reliance, filed 3/5/01 (Paper No. 16), upon Reichmann et al. (Nature 332: 323- (1988) (1449); is acknowledged.

However, the sequence provided in Reichmann et al. is directed towards a specific humanized CAMPATH-1 antibody, namely the rat IgG2a YTH 34.5HL antibody.

The claim is not limited to this particular rat IgG2a YTH 34.5HL humanized CAMPATH-1 antibody.

Applicant is invited to clarify the scope of the humanized CAMPATH-1 antibody set forth in claim 10; and address the biological deposit issues under 35 USC 112, first paragraph, for the enablement of the humanized CAMPATH-1 antibodies encompassed by the claimed invention.

Applicant's reliance upon the sequence of a particular rat IgG2a YTH 34.5HL humanized CAMPATH-1 antibody is not found persuasive, given the scope of the claimed invention.

9. Claims 2, 6-17, 22 and 25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 2, 6-17, 22 and 25 are indefinite in that the characteristics of the modified version of a therapeutic antibody and fragments thereof are ambiguous and unclear.

For example, independent claim 1 recites that the antibody is not a mixed molecule antibody having an H or L chain of the therapeutic antibody paired with and L or H chain of an unrelated antibody.

However the dependent claims recite and the specification discloses that the claims modified antibodies encompass humanized as well as chimeric antibodies. Therefore, the claims encompass recombinant antibodies comprising unrelated antibodies.

Also, given the absence of structural elements in the claims (e.g. amino acid sequences, deposited antibodies); the metes and bounds or defining characteristics of the claimed modified antibody versions encompassing modifications encompass both substantially the same sequences as well as alterations and substitutions are ambiguous, unclear and ill-defined.

Applicant's arguments, filed 3/5/01 (Paper No. 16), have been fully considered but are not found convincing for the reasons of record reiterated herein.

Applicant's cancellation of claim 1 is acknowledged.

Applicant asserts that the term "substantially" is not believed to render the claims indefinite.

However, given that the claims are ambiguous, unclear and ill-defined because the claims appear to be drawn to modifying a therapeutic antibody, which appear to encompass various recombinant antibodies (e.g. chimeric, humanized antibodies) derived from murine-human constructs and manipulations; and yet, the claims recite "not a mixed molecule", while the claims, including applicant's reliance on CAMPATH-1, appear to rely upon recombinant antibodies encompassing recombinant (e.g. mixed molecule) therapeutic antibodies. Given that all species use the same genetic code; an amino acid or amino acid sequence amino acid sequence is not necessarily human or not a mixed molecule antibody in nature.

Furthermore, the claims are relative in nature, which renders the claims indefinite. The nature and structural elements of the claims are not clearly defined by the claims and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Applicant's arguments are not found persuasive.

B) Claims 10 is indefinite in the recitation of "Campath-1 antibody" because its characteristics are not known. The use of "Campath-1" antibody as the sole means of identifying the claimed antibody and hybridoma renders the claim indefinite because this is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation s to define completely distinct antibodies or cell lines.

Applicant's arguments including the reliance upon Reichmann et al. (Nature 332: 323- (1988) (1449) in Paper No. 16, filed 3/5/01, is acknowledged.

However, the sequence provided in Reichmann et al. is directed towards a specific humanized CAMPATH-1 antibody, namely the rat IgG2a YTH 34.5HL antibody.

The claim is not limited to this particular rat IgG2a YTH 34.5HL humanized CAMPATH-1 antibody.

Applicant is invited to clarify the metes and bounds of the humanized CAMPATH-1 antibody set forth in claim 10.

Applicant's arguments are not found persuasive.

C) Claims 2, 6-17, 22 and 25 are indefinite in the recitation of "inducing immunological tolerance" because tolerance is an immunological phenomenon consisting of acquired incapacity of an individual to a particular antigen, which is a complex and multifaced phenomenon. Immunological tolerance can be induced in adult individuals by giving weak protein antigens either in repeated small doses or in large amounts (e.g. low-zone / high-zone tolerance). Given the various meanings of the term tolerance (complete lack of response to some level of response); given that tolerance is complex phenomenon and not necessarily achieved in humans; given that tolerance is a result of various methods and not necessarily a feature of a product per se; the metes and bounds of intended use or function of the claimed products for inducing tolerance is unclear and ill-defined.

Applicant's arguments, filed 3/5/01 (Paper No. 16), have been fully considered but are not found convincing.

Applicant asserts that it would be understood to mean a pretreatment with a given protein or molecule, irrespective of the mechanism, which results in diminished capacity to respond to that or to a further protein or molecule (mutant / wild type) without affecting response to unrelated antigens.

This definition of inducing tolerance is not readily apparent in the specification as filed, including the limitation of "diminished capacity to respond to a further protein or molecule (mutant / wild type)" versus the art recognizes that tolerance is drawn to a "specific incapacity" or "specific unresponsiveness" to specific antigens rather than a diminished response.

In addition, there is insufficient written support defining the metes and bounds of mutant and wild type antigens and how tolerance relates to them

Also given applicant's asserted definition of "diminished capacity to respond" rather than incapacity to respond; This asserted definition is relative in nature which renders the claims indefinite. This asserted definition is not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree and, in turn, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Applicant's arguments are not found persuasive.

D) The applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

10. The following of record is reiterated for applicant's convenience.

For examination purposes with respect to prior art issues and given the absence of structural limitations in the claims as well as the issues set forth above in the rejections under 35 USC 112, first and second, paragraphs; the claimed modified antibodies are encompassed by modified antibodies that have reduced affinity for their respective cell surface antigen specificity than its parent molecule.

The intended uses of the claimed products either as a therapeutic antibody or antibodies that induce immunological tolerance do not carry patentable weight per se. A composition is a composition irrespective of what its intended

The recitation of a process limitation in the instant claims is not seen as further limiting the claimed product, as it is presumed that equivalent products can be obtained by multiple routes. The burden is on the applicant to establish a patentable distinction between the claimed and referenced antibodies. The patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985) See MPEP 2113

11. Claims 2, 6-17, 22 and 25 are rejected under 35 U.S.C. § 102(e) as being anticipated by Waldmann et al. (U.S. Patent No. 5,846,534) (see entire document).

Applicant's arguments, filed 3/5/01 (Paper No. 16), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper No. 15.

Applicant submits that Waldmann et al. describe an antibody which binds effectively with the Campath-1 antigen, but does describe that the affinity of the antibody for the antigen is reduced to less than 50% of the affinity of the therapeutic antibody.

While it is acknowledged that Waldmann et al. is concerned with antibody that binds effectively with the Campath-1 antigen; the claims do not distinguish over the prior art antibodies; since both the prior art antibodies and the claimed antibodies would have the property of binding the Campath-1 antigen.

Waldmann et al. teach CAMPATH-1-specific antibodies and fragments thereof as well reshaping variable domains resulting in changes in antibody body (see Examples). In addition, Waldmann et al. Teach recycling the hypervariable regions on different human framework regions should change the idiotype (see column 4, paragraph 2). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and fragments thereof. It would have inherent in selecting and screening for humanized antibodies that the resultant antibodies would have had differing affinities, including those less than the native antibody. Also, fragments would have less affinity than the native molecule.

Applicant's arguments are not found persuasive.

12. Claims 2, 6-17, 22 and 25 are rejected under 35 U.S.C. § 102(e) as being anticipated by Crowe et al. (U.S. Patent No. 5,858,725) (see entire document).

Applicant's arguments, filed 3/5/01 (Paper No. 16), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper No. 15.

Applicant submits that Crowe et al. describe an antibody which binds effectively with the Campath-1 antigen, but does describe that the affinity of the antibody for the antigen is reduced to less than 50% of the affinity of the therapeutic antibody.

While it is acknowledged that Crowe et al. is concerned with antibody that binds effectively with the Campath-1 antigen; the claims do not distinguish over the prior art antibodies; since both the prior art antibodies and the claimed antibodies would have the property of binding the Campath-1 antigen.

In contrast to applicant's assertions, it does not appear that Crowe et al. is limited to importing only unmodified and unaltered CDRs; but rather Crowe et al. Does teach employing homologous variable regions as well (e.g.; see column 11, paragraph 6).

Crowe et al. teach preparation of humanized antibodies and fragments using recombinant strategies including the CAMPATH-1-specific antibody (e.g. Example 1). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and fragments thereof. It would have inherent in selecting and screening for humanized antibodies that the resultant antibodies would have had differing affinities, including those less than the native antibody. Also, fragments would have less affinity than the native molecule.

Applicant's arguments are not found persuasive.

13. Claims 2, 6-17, 22 and 25 are rejected under 35 U.S.C. § 102(e) as being anticipated by Carter et al. (U.S. Patent No. 6,054,297) (see entire document).

Applicant's arguments, filed 3/5/01 (Paper No. 16), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper No. 15.

Applicant submits that Carter et al. describe an antibody which binds effectively with the Campath-1 antigen, but does describe that the affinity of the antibody for the antigen is reduced to less than 50% of the affinity of the therapeutic antibody.

While it is acknowledged that Carter et al. is concerned with antibody that binds effectively with the Campath-1 antigen; the claims do not distinguish over the prior art antibodies; since both the prior art antibodies and the claimed antibodies would have the property of binding the Campath-1 antigen.

Carter et al. teach preparation of humanized antibodies and fragments using recombinant strategies including the CAMPATH-1-specific antibody (column 2, paragraph 4). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and fragments thereof. It would have inherent in selecting and screening for humanized antibodies that the resultant antibodies would have had differing affinities, including those less than the native antibody. Also, fragments would have less affinity than the native molecule.

Applicant's arguments are not found persuasive.

14. Claims 2, 6-8, 11-17, 22 and 25 are rejected under 35 U.S.C. § 102(b) as being anticipated by Isaacs et al. (Therapeutic Immunology 1: 303 -312, 1994; 1449) (see entire document, including the Abstract).

Applicant's arguments, filed 3/5/01 (Paper No. 16), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper No. 15.

Applicant submits that the instant claims were found novel over Isaacs et al. during the International Preliminary Examination of the current application

Contrary to applicant's assertions, an examiner is not prohibited from making a new grounds of rejection provided it is warranted during the prosecution of a patent application.

Here, the national phase prosecution is not limited by the International Preliminary Examination of the same or similar claims and the applicability of Isaacs et al. has been deemed applicable to the instant claims.

The claims do not distinguish over the prior art antibodies; since both the prior art antibodies and the claimed antibodies would have the property of binding an antigen.

Isaacs et al. teaching non-cell binding variants of therapeutic antibodies could be usefully exploited to generate therapeutic unresponsiveness to clinically useful antibodies. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies and fragments thereof.

Applicant's arguments are not found persuasive

15. Claims 2, 6-17, 22 and 25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over by Waldmann et al. (U.S. Patent No. 5,846,534) OR Crowe et al. (U.S. Patent No. 5,858,725) OR Carter et al. (U.S. Patent No. 6,054,297) in view of Isaacs et al. (Therapeutic Immunology 1: 303 -312, 1994; 1449).

Applicant's arguments, filed 3/5/01 (Paper No. 16), have been fully considered but are not found convincing essentially for the reasons of record set forth in Paper No. 15.

Applicant submits that the prior art is directed to modifying antibodies by maintaining their binding properties while reducing immunogenic responses to said modified antibodies.

Applicant submits that none of the prior art references deal with inducing tolerance to an individual nor to humanizing antibodies by removing binding abilities.

Applicant submits that the closes prior art would appear to be Isaacs et al.; however applicant further submits that Isaacs et al. Clearly teach against the use of non-cell binding, non-mixed molecule variants as a means of inducing tolerance (see page 310, column 1)

In contrast to applicant's assertions; this indication of no special advantage by Isaacs et al. was limited to a particular case of CBA.ca mice receiving the therapeutic antibody YTS 169.4 (also, see page 310, column 1).

Applicant's comments on mixed molecule and non-mixed molecule variants are acknowledged.

Given applicant's arguments; there appears some ambiguity as to the nature of the claimed limitations.

For example, it appears that applicant is relying upon the instant Examples which relies upon modifying humanized Campath-1 antibody, wherein said humanized Campath-1 would appear to be a mixed molecule by applicant's current assertions.

Also, given the use of the same genetic code by living things and that a particular sequence or amino acid residues are not limited to a particular molecule as well as the nature of the claims themselves; the claims do not necessarily read on a particular sequence or particular amino acid residues and the claims encompass various modifications to known antiobides or previously modified antibodies.

Applicant's assertions are in contrast with the clear teaching of Isaacs and Waldmann (H. Waldmann being a coinventor of the instant application), which is drawn to non-cell binding variants of therapeutic antibodies could be usefully exploited to generate therapeutic unresponsiveness to clinically useful antibodies (see entire document, including the Abstract).

For example this reference concludes (page 311, column 2, paragraph 2) by stating that:

Based upon a demonstration of T cell dependency of the anti-Ig response; we have devised regimes for inducing tolerance to cell-binding therapeutic mAbs. These are one- or two-step processes depending upon the characteristics of the therapeutic agent and these regimes might eventually be applied to the clinical situation. Our conclusions also suggest that some patients will be naturally tolerant of the at least some chimeric or humanized mAbs, and remain immunologically unresponsive upon repeated dosing.

One of ordinary skill in the art at the time the invention was made would have been motivated to select non-cell binding antibody variants, including fragments, of therapeutic antibodies, including the CAMPATH-1 antibody, to generate therapeutic unresponsiveness to clinically useful antibodies by a variety of recombinant means available to the ordinary artisan at the time the invention was made, as evidenced by Waldmann et al, Crowe et al. and Carter et al. Therefore the claimed limitations encompassing substitutions and alterations in sequences as well as reduced affinity would have been expected properties of selecting for non-cell binding variants of therapeutic antibodies at the time the invention was made. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
May 14, 2001